REMARKS

Summary Status of Office Action

Claims 1-11, 13, and 16-51 are pending, with claims 1, 5, 6, and 51 being independent. Claims 3, 4, 10, 11, 18-32, 34, 35, and 43-50 have been withdrawn from consideration as being drawn to non-elected subject matter. Claims 1-2, 5-9, 13, 16-17, 33, and 36-42 are under consideration, and all claims have been finally rejected.

Summary of Telephone Conferences with Examiner

Applicants express appreciation to Examiner Crouch for the May 23, 2005, and August 5, 2005, telephone conferences with Applicants' representative, Charles Niebylski, regarding the asserted new matter objection to the amendment filed January 27, 2005.

It was discussed that Applicants' January 27, 2005, amendment was filed in response to the "Notice of Non-compliance with nucleotide sequence rules" in the previous Office Action dated July 28, 2004, and issued by the previous Examiner, Ram Shukla. Further, it was noted that the symbol "v" in question was being used to amend a nucleotide sequence and not to amend an amino acid sequence, as asserted in the current Office Action. Also, it was pointed out that "v" is the compliant designation for a nucleotide base representing a base "other than t", as set forth in MPEP 2422, Table 3. Finally, it was pointed out that Applicants' specification does indeed provide support for the "v" base being a base other than t. The Examiner's attention was directed to the description of SEQ ID NO: 18 at page 7, lines 12-13, "wherein N represents a base other than T."

After being presented with this evidence, the Examiner indicated that it appeared that the amendment was appropriate and did not include new matter as asserted in the

objection. The Examiner requested that Applicants present the same evidence in the reply to the final Office Action, and indicate that the amendment in question was submitted to comply with the sequence listing requirements of MPEP 2422 and 37 CFR 1.821-1.825. Upon written presentation of such a reply, the Examiner indicated she would reconsider the objection and could see no reason at that time why she would not withdraw the objection.

Drawings and Information Disclosure Statement

Applicants express appreciation for acceptance of the drawings filed July 7, 2000, and for consideration of the Information Disclosure Statement (IDS) filed May 29, 2003.

Applicants note that documents U.S. Patent No. 5,877,399, U.S. Publication No. 2002/0019992, and WO 97/48792 submitted with the May 29, 2003, IDS were not initialed on the returned copy of the Form PTO-1449. Applicants respectfully request that the Examiner include a copy of the May 29, 2003, Form PTO-1449, with each of the four document entries initialed with the next communication from the U.S. Patent and Trademark Office. Applicants provide a convenience copy of the May 29, 2003, Form PTO-1449.

Objection under 35 U.S.C. §132(a)

The Examiner objects to the amendment filed January 27, 2005, because it allegedly introduces new matter into the disclosure without support for changing nucleotide "N" to nucleotide "V". The Examiner requests that Applicants cancel the alleged new matter in reply to the Office Action. Applications traverse the objection.

As indicated in the above Summary of the Telephone Conference with the Examiner, Applicants pointed out that the amendment was submitted to comply with sequence listing requirements of 37 C.F.R. 1.821-825, and that "v" is the compliant designation for a nucleotide base representing a base other than "t", as set forth in MPEP 2422, Table 3. Finally, it was pointed out that the Applicants' specification does indeed provide support for the "v" base being a base other than t. For example, the description of SEQ ID NO: 18 at page 7, lines 12-13, provides "wherein N represents a base other than T."

Accordingly, Applicants submit that the amendment filed January 27, 2005, does not add new matter, and respectfully request that the Examiner reconsider and withdraw the objection.

Rejection under 35 U.S.C. §112, first paragraph

Claims 1, 2, 5-9, 13, 16-17, 33, 36-42, and 51 remain rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The Office Action asserts that the claims contain subject matter that is not described in the specification in such as way as to enable one of skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention for reasons set for in the previous Office Actions dated November 8, 2002, July 30, 2003, and July 28, 2004. Applicants traverse the rejection for reasons of record, and as supplemented below.

Although the Office Action acknowledges that the specification teaches making a knockin transgenic mouse with an OS2 mutation, the Office Action asserts that one of skill in the art would not know how to use the transgenic mouse. The Office Action

alleges that Guo et al. (Nature Medicine 5: 101-106, 1999) "noted that a presenilin-1 knockin mouse did not show any signs of an overt mutant phenotype indicating that the targeted M146 mutation does not impair normal development and physiological functions of presenilin-1, although the mouse did show signs of hypersensitivity to seizure-induced synaptic degeneration and necrotic neuronal death in the hippocampus, when the adult mouse was administered excitotoxin kainite." The Office Action asserted that Guo indicates that a presenilin-1 knockin mouse would require treatment with an agent for its use, and the present specification does not teach the phenotypes of the claimed knockin animals. Given Guo and the alleged unpredictability of the art of transgenesis, the Office Action alleges that one of skill in the art would not know the phenotypes of the knockin animal encompassed by the claimed invention and therefore would not know how to use them.

In response, Applicants note that as disclosed in the Guo document, and known to one of ordinary skill in the art, a presenilin-1 knockin mouse does not show an "overt mutant phenotype" because the "mutation does not impair normal development and physiological functions of presenilin-1." The hypersensitivity reaction disclosed in Guo is induced by administration of excitotoxin kainite and is a drug effect, rather than a phenotype that is a result of a targeted M146 mutation. Applicants note that the claimed knockin animal has the phenotype of "overexpression of Amyloid β42 in the brain of said mouse," and that this particular phenotype is described, for example, in Applicants' publication Nakano Y. et al., Eur. J. Neurosci. 11:2577-2581, 1999, previously submitted in the Information Disclosure Statement filed May 29, 2003. Further, Applicants provide copies of Yasuda, Y., et al., Biochim Biophys Res Commun

296:313-318, 2002, and Katayama, T., et al., J. Biol. Chem. 276:43446-43454, 2001, which indicate that familial Alzheimer's disease-linked presenilin-1 mutations disturbs activation of endoplasmic reticulum stress transducers. Applicants submit that these changes in the mutant animal would be considered by the skilled artisan to be a developed phenotype in the claimed animal. Accordingly, Applicants submit that these references provide evidence of the predictability of preparing and using the claimed presenilin-1 mutants, and indicates that specification enables one of skill in the art to make and use the claimed invention.

It was commonly known to one of ordinary skill in the art at the time of filing that the overexpression of Amyloid β42 in the brain is one of the causes of Alzheimer's disease, and therefore, one of ordinary skill in the art would have understood that the claimed knockin mouse could be used for laboratory research of Alzheimer's disease, and for screening of a substance having therapeutic activity for treatment of Alzheimer's disease. The overexpression of Amyloid β42 in the brain of the claimed knockin mouse would be a phenotype that would be recognized by one of ordinary skill in the art, and one of ordinary skill in the art would easily recognize such a phenotype given knowledge in the art of the corresponding PS-1 mutation in humans.

Furthermore, in combination with the above knowledge, one of ordinary skill in the art would know that the specification enables the claimed invention. For example, the specification at the paragraph bridging pages 10-11 discloses a method for evaluating a substance useful for therapeutic and/or preventive treatment of a disease involving overexpression of Amyloid β42 in the brain which comprises the step of subjecting the aforementioned gene-mutated animal which is administered with a test

substance in comparison to a gene-mutated animal not administered with the test compound. The specification at pages 10-11 describes that the evaluation may involve a comparison conducted by using a memory learning test, a pathological test, a pathological test based on neuropathology in a peripheral portion of the cerebral cortex in which one or more items selected from the group consisting of suppression of decrease in overgrown gliosis in a peripheral portion of the cerebral cortex of the brain, suppression of decrease in uptake of 2-deoxyglucose in a peripheral portion of the cerebral cortex of the brain, and suppression of decrease in availability of 2-deoxyglucose in the cerebral cortex of the brain. Additionally, the evaluation may involve a comparison conducted for survival period of time, exploratory behavior and migratory behavior.

In addition, for example, the specification at page 14, second paragraph, discloses that the claimed knockin gene-mutated mouse has a characteristic feature of producing amyloid β protein in a larger amount in comparison to a normal animal due to the genetic mutation. The increased amount of amyloid β protein may be sufficient for "recognition of a substantial difference in the evaluation of degrees of memory disorder, pathological observations, and various neural disorders as compared to a normal animal."

Therefore, it is within the scope of common technical knowledge of one of ordinary skill in the art, and one of ordinary skill in the art would understand, from the abundant guidance set forth in Applicants' specification, how to obtain the claimed knockin gene-mutated mouse, primary cell culture or a subcultured cell obtainable by isolating a cell from such gene-mutated mouse, and methods for evaluating the

therapeutic effect or preventive treatment of a substance on Alzheimer's disease related to overexpression of Amyloid β42 in the brain comprising administering a test substance to a gene-mutated mouse.

For these reasons, Applicants' claims are enabled, and the rejection of claims 1, 2, 5-9, 13, 16-17, 33, 36-42, and 51 under 35 U.S.C. §112, first paragraph should be withdrawn.

CONCLUSION

For the reasons advanced above, Applicants respectfully submit that all pending claims patentably define Applicants' invention. Allowance of the application with an early mailing date of the Notices of Allowance and Allowability is therefore respectfully requested.

Respectfully Submitted,
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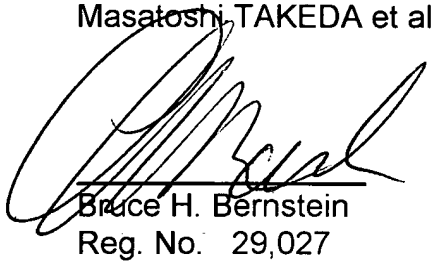

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August 18, 2005
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